Birth Defects from Impaired Glucose Metabolism

Among women without diabetes before pregnancy, **impaired glucose metabolism during pregnancy** is associated with risk of **major congenital malformations** of the heart, central nervous system, musculoskeletal system, and all birth defects combined.

General Information	
Broad Focus Area	Undesirable outcomes of pregnancy: birth defects and preterm birth
Background and Justification	Among women who have type 1 or type 2 diabetes before pregnancy, the risk of congenital anomalies in offspring is increased, and animal models confirm the teratogenicity of impaired glucose metabolism. Whether women first diagnosed with diabetes during pregnancy (gestational diabetes) or those with lesser degrees of impaired glucose metabolism during pregnancy have offspring with increased frequency of birth defects has not been determined, though limited data suggest an association.[1,2]
Prevalence/ Incidence	Major congenital malformations of the heart, central nervous system, and musculoskeletal system are among the most common defects seen in offspring of diabetic women. The general prevalence of targeted birth defects is: 0.6% of births with major congenital malformations of the heart[3] 0.3% of births with central nervous system defects[4] 0.2% of births with musculoskeletal birth defects[4] 3-4% of births with major birth defects combined[5,6] The total prevalence of diabetes in women aged 20-39 years is 1.7% and 6% among those aged 40-49 years.[7] Among reproductive-aged women with diabetes, about one-third (35.4%) of women younger than 40 years and about one-quarter (26.7%) of those aged 40 years or older did not know that they had the disease.[7] About 4-7% of pregnancies are complicated by gestational diabetes.[8] Assuming Impaired Glucose Tolerance is of two types 1) "impaired fasting glucose (IFG)" or 2) "impaired glucose tolerance (IGT)," depending on the test used to diagnose it: - In a cross-section of U.S. adults aged 40 to 74 years tested from 1988 to 1994, 33.8 percent had IFG, 15.4 percent had IGT, and 40.1 percent had pre-diabetes (IGT or IFG or both). Applying these percentages to the 2000 U.S. population, about 35 million adults aged 40 to 74 would have IFG, 16 million would have IGT, and 41 million would have pre-diabetes.[9] - Based on data from the 1999-2000 National Health and Nutrition Examination Survey, approximately 2% of U.S. adults between 20 and 39 years of age are affected by impaired fasting glucose, a type of impaired glucose metabolism.[10]
Economic Impact	The estimated lifetime cost of birth defects, among children born during one year in the U.S., is $2 billion for heart defects, central nervous defects, and musculoskeletal defects combined, and $8 billion (1992 dollars) for all birth defects combined).[11]

Exposure Measures			Outcome Measures	
Primary/ Maternal	Maternal report of gestational diabetes: Blood glucose and HgbA1C		***Primary/ Maternal***	Prenatal assessment of birth defects

	- Oral glucose tolerance test (potential study procedure) - Serum lipid profile - Serum insulin or related sample (e.g., C-peptide) - Genetic sample (for exploration of potentially relevant genes such as VNTR insulin, glucokinase			
Methods	- Blood samples - Medical record review		Methods	Ultrasound
Life Stage	Preconception and prenatal		Life Stage	Prenatal
Primary/Child	- Serum glucose - Serum insulin or related sample (e.g., C-peptide) - Genetic sample (for exploration of potentially relevant genes such as VNTR insulin, glucokinase)		***Primary/Child***	Assessment for birth defects: - Standard physical examinations - Neurological examination
Methods	- Blood samples - Physical exam		Methods	Direct observation by a medical professional or via medical record review
Life Stage	Birth		Life Stage	Birth through age 20
Secondary/ Maternal			***Secondary***	
Methods			Methods	
Life Stage			Life Stage	

Important Confounders/Covariates	
Previous history of birth defect	Mothers of first child with birth defect are 2.4 times more likely than other women to have a second infant with a birth defect; most of the risk is accounted for by the same defect.[12]
HgbA1C	Low HgbA1C is associated with reduced incidence of congenital abnormalities.[13]
Lipid profile	Maternal fat-modified diets result in lower total and HDL cholesterol in infants and could be a suitable way to prevent cardiovascular disease among infants from the beginning of life.[14]
Insulin gene VNTR	There is some conflicting information regarding this insulin gene. Most data suggest that VNTR variations do not influence early growth; some data suggest an increased risk of childhood obesity and insulin resistance.[15, 16, 17]
Glucokinase mutation	The intrauterine environment is associated with insulin resistance in childhood. Birth weight is reduced if one parent has a glucokinase mutation.[18]
Hormone levels such as cortisol	Fetuses exposed to glucocorticosteroids (GCS) in the first trimester had a lowed median birth weight and were born at an earlier gestational age, but did not exhibit an increased teratogenic risk.[19]
Smoking status	The more a pregnant woman smokes, the greater the risk to her baby. Both nicotine and carbon monoxide play a role in causing adverse

	pregnancy outcomes.[20, 21, 22, 23, 24]
Use of medication	Anticonvulsants can cause serious problems in the developing fetus, including mental retardation and slow growth. Other drugs associated with birth defects include antipsychotic and antianxiety agents, certain antibiotics.[25]
Family History	About 20% of birth defects are hereditary, resulting from the interaction of genes from one or both parents plus environmental influences. Defects may include cleft lip and palate, spina bifida, heart defects.[25, 26]
Other factors	Recreational drugs have been associated with arm and leg abnormalities and central nervous system problems.[25]

Population of Interest		Estimated Effect that is Detectable
Women with and without diabetes prior to pregnancy and their offspring		Assuming 100,000 infants are born into the study, with a prevalence of gestation diabetes of 5%: Smallest detectable relative risks for heart defects ~ 1.6 Smallest detectable relative risks for central nervous system defects ~ 1.8 Smallest detectable relative risks for musculoskeletal defects ~ 2.1

Other Design Issues	
Ethical/Burden Considerations	Potential for Oral Glucose Tolerance Test as part of study protocol
Cost/Complexity of Data Collection	Diabetes status prior to pregnancy may be unknown for currently pregnant women who enter the sample

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